

# Bladder Relaxant Preparations Review

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## Bladder Relaxant Preparations Review

### **FDA-Approved Indications**<sup>1,2,3,4,5,6,7,8,9,10,11</sup>

| <b>Drug</b>  | <b>Manufacturer</b> | <b>Indication(s)</b>  |
|--|---------------------|---|
| darifenacin<br>(Enablex <sup>®</sup> )                   | Novartis            | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| fesoterodine ER<br>(Toviaz <sup>™</sup> )                | Pfizer              | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| oxybutynin<br>(Ditropan <sup>®</sup> )                   | generic             | Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)  |
| oxybutynin ER<br>(Ditropan <sup>®</sup> XL)              | generic             | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency<br><br>Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) |
| oxybutynin hydrochloride gel<br>(Gelnique <sup>™</sup> ) | Watson              | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| oxybutynin transdermal<br>(Oxytrol <sup>™</sup> )        | Watson              | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| solifenacin<br>(VESIcare <sup>®</sup> )                  | Astellas            | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency  |
| tolterodine<br>(Detrol <sup>®</sup> )                    | Pfizer              | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| tolterodine ER<br>(Detrol <sup>®</sup> LA)               | Pfizer              | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency  |
| tropium<br>(Sanctura <sup>®</sup> )                      | Allergan            | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency  |
| tropium ER<br>(Sanctura <sup>®</sup> XR)                 | Allergan            | Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency  |

## Overview

Overactive bladder (OAB) is a chronic and debilitating syndrome that is characterized by urinary urgency with or without urge incontinence, usually in combination with urinary frequency (eight or more voiding episodes per 24 hours) and nocturia (awakening one or more times per night to void).<sup>12</sup> The patient fear of urinary incontinence (driven by embarrassment and social stigma) can result in significant changes to a patient's quality of life (QoL). The overall prevalence of OAB occurs equally in men (16 percent) and women (16.9 percent); however, more women suffer from OAB with incontinence.<sup>13</sup> The incidence of women experiencing urge urinary incontinence (UUI) monthly or more often is five to ten percent of adult women.<sup>14</sup> The prevalence of OAB is almost 20 percent in those older than 60 years of age.

Many conditions are associated with the symptoms of OAB including lower urinary tract conditions (e.g., urinary tract infection, obstruction), neurological conditions (e.g., stroke, Alzheimer's disease), systemic conditions (e.g., heart failure, vascular insufficiency), functional and behavioral conditions (e.g., impaired mobility), and use of various medications (e.g., diuretics, narcotics). In addition, OAB and urinary incontinence are associated with skin infections and irritations, and, in the elderly, an increased risk of falls and fractures.<sup>15,16,17</sup>

In the resting state, the pressure within the bladder is lower than urethral resistance. In the normal individual, the bladder can hold between 350 and 500 mL with the first urge to urinate occurring when the bladder contains around 200 mL. Urination occurs following a sequence of events that begins with a decrease in urethral resistance. Subsequently, the layered smooth muscle that surrounds the bladder (the detrusor muscle) contracts causing the bladder to empty. This sequence of events begins when the bladder's sensory stretch receptors are activated thereby sending signals from the spinal cord to brain centers, resulting in the sensation of urge due to increased bladder filling.<sup>18</sup>

The symptoms of OAB are usually associated with overactivity of the detrusor muscle as it contracts spastically, sometimes without a known cause. This results in sustained high bladder pressure and urgency or urge incontinence depending on the sphincter response.<sup>19</sup>

The management of OAB includes both pharmacological and non-pharmacological (e.g., bladder training, pelvic floor muscle exercises) interventions.<sup>20,21</sup> Antimuscarinic agents that relax the detrusor or prevent a bladder contraction are effective for OAB.

In August 2009, the Agency for Healthcare Research and Quality (AHRQ) released an evidence-based review on the treatment of overactive bladder (OAB), urge urinary incontinence and related symptoms in women.<sup>22</sup> The AHRQ stated that all pharmacologic treatments are effective at improving one or more of the symptoms of OAB when compared to placebo. No single drug was definitively superior to others by a preponderance of evidence including a comparison of newer selective agents to the older antimuscarinic agents.

## Pharmacology

Contractility of the human detrusor muscle is predominantly controlled by the parasympathetic nervous system. Although other neurotransmitter pathways are involved, acetylcholine is the major peripheral neurotransmitter responsible for bladder contraction. Acetylcholine causes this response through its interaction with muscarinic receptors located on the detrusor muscle.<sup>23,24</sup> There are five known muscarinic receptor subtypes labeled M<sub>1</sub> through M<sub>5</sub>. Although the detrusor muscle contains a greater number of M<sub>2</sub> than M<sub>3</sub> receptors (3:1 ratio), it appears that

M<sub>3</sub> receptors are primarily responsible for normal micturition contraction. In addition to their role in bladder contraction, the M<sub>2</sub> and M<sub>3</sub> muscarinic receptor subtypes are involved in contraction of gastrointestinal smooth muscle, saliva production, central nervous system function, cardiac function, and iris sphincter function.

In general, antimuscarinic drugs depress both voluntary and involuntary bladder contractions. Antimuscarinic action on the lower urinary tract results in an increase in residual urine, reflecting an incomplete emptying of the bladder and a decrease in detrusor pressure.

Oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol) is a tertiary amine ester that is a potent, nonselective, competitive muscarinic receptor antagonist. Oxybutynin's effects on the detrusor muscle are mediated via M<sub>3</sub> receptors. Because it is a non-selective antimuscarinic, oxybutynin may produce adverse effects consistent with anticholinergic actions in the central nervous system (CNS), parotid gland, and gastrointestinal (GI) tract. Oxybutynin also possesses minor local anesthetic properties.

The tertiary amine tolterodine (Detrol, Detrol LA) and its active metabolite, 5-hydroxymethyl tolterodine, are also competitive muscarinic receptor antagonists. Tolterodine shows selectivity for the urinary bladder over salivary glands. Neither tolterodine nor its active metabolite exert clinically significant effects on other neurotransmitter receptors or other pharmacologic targets such as calcium channels.<sup>25,26</sup>

Fesoterodine ER (Toviaz) is rapidly and extensively hydrolyzed to its active metabolite, 5-hydroxymethyl tolterodine. Both are non-selective competitive antagonists of muscarinic M<sub>1</sub> through M<sub>5</sub> receptors. The active metabolite has greater potency than the parent compound.<sup>27,28</sup> In contrast to tolterodine, the conversion of fesoterodine to its metabolite bypasses the CYP system, although CYP3A4 and CYP2D6 are involved in subsequent inactivation of the active metabolite.

Trospium (Sanctura, Sanctura XR) is an antispasmodic, competitive antimuscarinic agent that has high affinity for the M<sub>1</sub>, M<sub>2</sub>, and M<sub>3</sub> receptor subtypes with lower affinity for the M<sub>4</sub> and M<sub>5</sub> receptors.<sup>29</sup> When used at therapeutic doses, trospium has negligible affinity for nicotinic receptors. Trospium is a hydrophilic quaternary amine and does not cross the blood-brain barrier or conjunctiva like oxybutynin, a tertiary amine; this reduces the risk of CNS-related adverse effects such as sedation and dizziness.<sup>30,31</sup>

Darifenacin (Enablex) is a competitive muscarinic receptor antagonist. It is a selective antagonist at M<sub>3</sub> receptors.<sup>32,33</sup> In contrast to the non-selective agents, darifenacin has been reported to have selectivity for the bladder over the salivary gland *in vivo*. It is not clear if selective antagonism at the M<sub>3</sub> receptor improves patient tolerability or clinical efficacy versus currently available agents.

Solifenacin (VESIcare) is a competitive M<sub>3</sub>-selective muscarinic receptor antagonist but has some effect on all muscarinic receptors.<sup>34</sup> Solifenacin has functional selectivity for the bladder compared to salivary muscarinic receptors; therefore, the antimuscarinic effects of solifenacin on the salivary gland are less pronounced. Due to its poor CNS penetration, CNS adverse effects are minimal.

**Pharmacokinetics**<sup>35,36,37,38,39,40,41,42,43,44,45</sup>

| Drug                             | Time to Peak (hr) | Route of Metabolism           | Half-life (hr)        |
|----------------------------------|-------------------|-------------------------------|-----------------------|
| darifenacin (Enablex)            | 6.49-7.61         | CYP2D6 <sup>††</sup> , CYP3A4 | 13-19                 |
| fesoterodine ER (Toviaz)         | 5                 | CYP2D6, CYP3A4                | 7.31-8.59             |
| oxybutynin (Ditropan)            | <1                | CYP3A4                        | 2-3                   |
| oxybutynin ER (Ditropan XL)      | 11.8-12.7         | CYP3A4                        | 12.4-13.2             |
| oxybutynin gel (Gelnique)        | n/a               | CYP3A4 <sup>*</sup>           | 64                    |
| oxybutynin transdermal (Oxytrol) | 10-48             | CYP3A4 <sup>*</sup>           | 7-8                   |
| solifenacin (VESIcare)           | 3-8               | CYP3A4                        | 45-68                 |
| tolterodine (Detrol)             | 1-2               | CYP2D6, CYP3A4                | 2-2.2 <sup>†</sup>    |
| tolterodine ER (Detrol LA)       | 2-6               | CYP2D6, CYP3A4                | 6.9-8.4 <sup>**</sup> |
| trospium (Sanctura)              | 5-6               | Ester hydrolysis              | 18.3                  |
| trospium ER (Sanctura XR)        | 5                 | Ester hydrolysis              | 36                    |

\* transdermal route reduces CYP3A4 metabolism in the liver and gut

† half-life of tolterodine tablets can be up to 9.6 hours in slow metabolizers

\*\* half-life of tolterodine extended-release capsules can be up to 18 hours in slow metabolizers

†† bioavailability of darifenacin is increased by 77 to 131 percent in poor metabolizers of CYP2D6

After oral administration, tolterodine (Detrol, Detrol LA) is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. This metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Like tolterodine, the 5-hydroxymethyl metabolite exhibits a high specificity for muscarinic receptors.

Like tolterodine, fesoterodine (Toviaz) is rapidly and extensively hydrolyzed to the 5-hydroxymethyl tolterodine, the active metabolite which is responsible for its antimuscarinic activity. With virtually the entire moiety converted to the active metabolite, fesoterodine functionally acts as a prodrug. In addition, its conversion to 5-hydroxymethyl tolterodine bypasses the CYP system, unlike tolterodine.

Administration of trospium (Sanctura) with a high fat meal reduces absorption, thus reducing bioavailability by 70 to 80 percent. Administration of trospium ER (Sanctura XR) immediately after a high-fat content meal reduced the oral bioavailability by 35 percent and the  $C_{max}$  by 60 percent. It is recommended that trospium and trospium ER be taken on an empty stomach.

**Contraindications/Warnings**<sup>46,47,48,49,50,51,52,53,54,55,56</sup>

All of the bladder relaxants are contraindicated in patients with uncontrolled narrow-angle glaucoma or gastric and/or urinary retention. All bladder relaxants are also contraindicated for patients with hypersensitivity to the primary drug or its ingredients.

All of the bladder relaxants should be used with caution in patients with obstruction of the gastrointestinal tract, intestinal atony, megacolon, myasthenia gravis, paralytic ileus, severe colitis, and obstructive uropathy.

Transfer of oxybutynin to another person can occur when vigorous skin-to-skin contact is made with the application site can occur with the use of the transdermal gel (Gelnique). To minimize this potential, patients should cover the application site with clothing after the gel has dried if direct skin-to-skin contact at the application site is anticipated. Patients should wash their hands immediately after application of the gel.

Alcohol should not be consumed within two hours of trospium ER (Sanctura XR).

**Drug Interactions**

darifenacin (Enablex)<sup>57</sup>

Darifenacin metabolism is primarily mediated by CYP2D6 and CYP3A4. Inducers of CYP3A4 or inhibitors of either enzyme may alter the pharmacokinetics of darifenacin. No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.

The daily dose of darifenacin should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, and nefazodone).

Caution is recommended when darifenacin is used concomitantly with medications that have a narrow therapeutic index and that are primarily metabolized by CYP2D6 (such as tricyclic antidepressants). Administration of imipramine with darifenacin results in a 70 percent increase in bioavailability of the antidepressant.

fesoterodine ER (Toviaz)<sup>58</sup>

Doses of fesoterodine ER greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors such as such as ketoconazole, itraconazole, and clarithromycin. Induction of CYP3A4 may lead to reduced plasma levels. No dosage adjustments are necessary in the presence of CYP3A4 inducers.

Interactions with CYP2D6 inhibitors have not been studied, however no dosage adjustments are recommended in the presence of CYP2D6 inhibitors.

oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol)<sup>59,60,61,62</sup>

Concomitant use of oxybutynin with other anticholinergic agents or other agents that cause dry mouth, constipation, somnolence, or other anticholinergic-like effects may increase the frequency or severity of these effects. Anticholinergic agents may alter the absorption of some medications due to their effects on GI motility.

### solifenacin (VESIcare)<sup>63</sup>

Solifenacin is a substrate of CYP3A4. Inhibitors or inducers of CYP3A4 may alter the pharmacokinetics of solifenacin. Coadministration with ketoconazole, a potent CYP3A4 inhibitor, increases the bioavailability of solifenacin by 100 to 170 percent. It is recommended not to exceed a 5 mg daily dose of solifenacin when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.

### tolterodine (Detrol, Detrol LA)<sup>64,65</sup>

Fluoxetine, a potent inhibitor of CYP2D activity, significantly inhibits the metabolism of tolterodine. The result is a 4.8-fold increase in tolterodine area-under the curve (AUC), a 52 percent decrease in  $C_{max}$ , and a 20 percent decrease in AUC of the 5-hydroxymethyl metabolite. The sums of unbound serum concentrations of tolterodine and its metabolite are only 25 percent higher during the interaction; no dose adjustment is required.

In the presence of ketoconazole, the mean  $C_{max}$  and AUC of tolterodine increases by 2- and 2.5-fold, respectively, in poor metabolizers. Based on these findings, other potent CYP3A4 inhibitors such asazole antifungals, macrolide antibiotics, cyclosporine, or vinblastine may also lead to increases of tolterodine plasma concentrations.

### trospium (Sanctura, Sanctura XR)<sup>66,67</sup>

Trospium has not been associated with clinically relevant drug-drug interactions. It does have the potential to interact with other drugs that are eliminated by active tubular secretion (e.g., pancuronium, procainamide, morphine, metformin, vancomycin, and tenofovir). Monitoring is recommended in patients receiving trospium and a drug eliminated in this manner.

**Adverse Effects**

| Drug  | Constipation | Diarrhea | Dry mouth   | Dyspepsia | Dizziness |
|---|--------------|----------|-------------|-----------|-----------|
| darifenacin 15 mg (Enablex) <sup>68</sup>                 | 14.8 - 21.3  | 0.9-2.1  | 20.2 - 35.3 | 2.7 - 8.4 | 0.9 - 2.1 |
| fesoterodine ER (Toviaz) <sup>69</sup>                    | 4.2-6        | nr       | 18.8-34.6   | 1.6-2.3   | nr        |
| oxybutynin 5-20 mg (Ditropan) <sup>70</sup>               | 15.1         | 1 - < 5  | 71.4        | 6         | 16.6      |
| oxybutynin ER 5-30 mg (Ditropan XL) <sup>71</sup>         | 13           | 9        | 61          | 7         | 6         |
| oxybutynin gel 1 sachet/day (Gelnique) <sup>72</sup>      | 1.3          | nr       | 1.9-7.5     | nr        | 1.5-2.8   |
| oxybutynin transdermal 3.9 mg/day (Oxytrol) <sup>73</sup> | 3.3          | 3.2      | 4.1-9.6     | nr        | nr        |
| solifenacin 10 mg (VESIcare) <sup>74</sup>                | 5.4-13.4     | nr       | 10.9-27.6   | 1.4-3.9   | 1.8-1.9   |
| tolterodine 4 mg (Detrol) <sup>75</sup>                   | 7<br>(4)     | 4<br>(3) | 35<br>(10)  | 4<br>(1)  | 5<br>(3)  |
| tolterodine ER 4 mg (Detrol LA) <sup>76</sup>             | 6<br>(4)     | reported | 23<br>(8)   | 3<br>(1)  | 2<br>(1)  |
| tropium 40 mg (Sanctura) <sup>77</sup>                    | 9.6          | nr       | 20.1        | 1.2       | nr        |
| tropium ER 60 mg (Sanctura XR) <sup>78</sup>              | 8.5          | nr       | 10.7        | 1.2       | nr        |

Adverse effects are reported as a percentage. Adverse effects data are obtained from the package insert information and are not meant to be comparative. Incidences for placebo group are indicated in parentheses. nr = not reported.

All the agents in this class are anticholinergics and accordingly have the expected adverse effects of dry mouth and constipation. The incidences of the adverse effects are higher with immediate release products but still demonstrated to a lesser degree with extended-release products. The withdrawal rates in trials due to the adverse effects for drugs were similar among all available agents although there is a lack of direct comparative data.

Pruritis at the transdermal oxybutynin (Oxytrol) application site occurs in 14 to 17 percent of patients treated with the oxybutynin transdermal patch.<sup>79,80</sup> Pruritis at the application site for the topical oxybutynin gel was reported in one to two percent of patients while overall application site reactions occurred in two to six percent of patients. Application site reaction for oxybutynin gel was the most common reason for patient discontinuation of the medication.<sup>81</sup>



**Special Populations**<sup>82,83,84,85,86,87,88,89,90,91,92</sup>

Pediatrics

Oxybutynin (immediate-release tablets and syrup) are approved for use in pediatric patients ages five years and older, and oxybutynin extended-release tablets are approved for use in pediatric patients six years and older with symptoms of detrusor activity associated with neurological condition. The safety and efficacy of darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin gel (Gelnique), oxybutynin transdermal (Oxytrol), solifenacin (Vesicare), trospium (Sanctura), and trospium ER (Sanctura XR) in pediatric patients have not been established. Efficacy data are not available for tolterodine and tolterodine ER (Detrol, Detrol LA).

Pregnancy

Oxybutynin is Pregnancy Category B. The other drugs in this class are Pregnancy Category C. Darifenacin, oxybutynin, solifenacin, fesoterodine, tolterodine, and trospium should only be used during pregnancy if the benefit to the mother outweighs the potential risk to the fetus.

Geriatric Use

No overall differences in safety or efficacy have been observed between patients over 65 year of age and younger patients with darifenacin, solifenacin, tolterodine, trospium, and fesoterodine. However, in clinical studies, the incidence of adverse effects with trospium and fesoterodine among elderly patients aged 75 years and older was higher compared to younger patients.

In general for oral oxybutynin, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range reflecting the greater frequency of concomitant diseases or other drug therapy. While no overall differences in safety and efficacy with oxybutynin gel or transdermal dosage forms were noted between younger and elderly patients, greater sensitivity of older individuals cannot be ruled out.

Hepatic Insufficiency

All of the oral agents in this class require some caution or dosage adjustment in patients with hepatic impairment. See the dosage chart. There is no experience with the use of oxybutynin in patients with hepatic insufficiency.

Renal Insufficiency

Darifenacin is the only oral agent in this class that does not require caution or dosage adjustment in patients with renal impairment. There is no experience with the use of oxybutynin in patients with renal insufficiency.

Trospium ER is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/minute).

**Dosages**

| <b>Drug</b>                                    | <b>Usual Dose</b>                      | <b>Patients with Hepatic and/or Renal Dysfunction</b>                                     | <b>Availability</b>                                 |
|--|--|---|---|
| darifenacin (Enablex) <sup>93</sup>            | 7.5 to 15 mg daily                     | 7.5 mg daily (for moderate hepatic dysfunction only)                                      | 7.5, 15 mg ER tablets                               |
| fesoterodine ER (Toviaz) <sup>94</sup>         | 4 to 8 mg daily                        | 4mg daily (for severe renal insufficiency), not recommended for severe hepatic impairment | 4, 8 mg ER tablets                                  |
| oxybutynin (Ditropan) <sup>95</sup>            | 5 mg two or three times daily          | --  | 5 mg tablet<br>5 mg/mL oral solution                |
| oxybutynin ER (Ditropan XL) <sup>96</sup>      | 5 to 10 mg daily                       | --  | 5, 10, 15 mg ER tablets                             |
| oxybutynin gel (Gelnique) <sup>97</sup>        | contents of one sachet applied per day | --  | 1 gm (1.14mL) of 100 mg/g oxybutynin gel per sachet |
| oxybutynin transdermal (Oxytrol) <sup>98</sup> | one patch applied twice weekly         | --  | 3.9 mg/24 hrs transdermal patch                     |
| solifenacin (VESicare) <sup>99</sup>           | 5 to 10 mg daily                       | 5 mg daily  | 5, 10 mg tablets                                    |
| tolterodine (Detrol) <sup>100</sup>            | 2 mg twice daily                       | 1 mg twice daily  | 1, 2 mg tablets                                     |
| tolterodine ER (Detrol LA) <sup>101</sup>      | 4 mg daily                             | 2 mg daily  | 2, 4 mg ER capsules                                 |
| tropium (Sanctura) <sup>102</sup>              | 20 mg twice daily                      | 20 mg daily (for severe renal impairment only)  | 20 mg tablet  |
| tropium ER (Sanctura XR) <sup>103</sup>        | 60 mg daily in the morning             | Not recommended for severe renal impairment   | 60 mg ER capsule                                    |

For pediatric patients over five years of age, oxybutynin immediate-release tablets or syrup are given at a dosage of 5 mg two times per day. The maximum recommended dose is oxybutynin 5 mg three times a day. For pediatric patients six years of age and older, the recommended starting dose of oxybutynin extended-release tablets is 5 mg once daily. The dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

Oxybutynin gel should be applied to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Rotate application sites, avoiding use of the same site on consecutive days.

**Clinical Trials****Search Strategy**

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized,

controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

### darifenacin (Enablex) versus placebo

A multicenter, double-blind, parallel-group study enrolled 561 patients (ages 19 to 88 years; 85 percent female) with OAB symptoms for at least six months into a 12-week study.<sup>104</sup> After washout and a two-week placebo run-in, patients were randomized (1:4:2:3) to darifenacin 3.75, 7.5, or 15 mg tablets or placebo, each given once daily. Darifenacin 7.5 and 15 mg had a rapid onset of effect with significant improvement compared with placebo for most parameters at the first evaluation at week two. At the conclusion of the study, the number of incontinence episodes per week was reduced from baseline by 67.7 percent with darifenacin 7.5 mg and 72.8 percent with darifenacin 15 mg compared with 55.9 percent with placebo ( $p=0.010$  and  $0.017$ , respectively, versus placebo). The darifenacin 3.75 mg group was included for proof of concept of dose flexibility; therefore, formal sample sizing and statistical analysis were not performed for this group. Darifenacin 7.5 and 15 mg, respectively, were significantly superior to placebo for improvements in micturition frequency (both  $p<0.001$ ), bladder capacity ( $p<0.040$ ,  $p<0.001$ ), frequency of urgency ( $p<0.001$ ,  $p=0.005$ ), severity of urgency ( $p<0.001$ ,  $p=0.002$ ), and number of incontinence episodes leading to a change in clothing or pads ( $p<0.001$ ,  $p=0.002$ ). There was no significant reduction in nocturnal awakenings due to OAB. The most common adverse events were mild to moderate dry mouth and constipation. No patients withdrew from the study as a result of dry mouth, and discontinuation related to constipation was rare ( $<1$  percent). There were no reports of blurred vision, and the safety profile was comparable to placebo.

### fesoterodine (Toviaz) versus tolterodine ER (Detrol LA)

A multicenter, double-blind, placebo- and active-controlled trial with tolterodine ER was performed to assess the efficacy and safety of fesoterodine.<sup>105</sup> Subjects, at least 18 years of age, with a history of OAB greater than six months and increased micturition frequency and urgency and/or urgency urinary incontinence (UUI), were randomized to placebo ( $n=279$ ), fesoterodine 4 mg ( $n=265$ ), fesoterodine 8 mg ( $n=276$ ), or tolterodine ER 4 mg ( $n=283$ ) for 12 weeks. The primary efficacy endpoint was a change from baseline to week 12 in micturitions per 24 hours. At the end of treatment, the mean number of micturitions per 24 hours significantly reduced from baseline in all active drug groups compared to placebo ( $-1.73$  tolterodine ER,  $-1.76$  fesoterodine 4 mg, and  $-1.88$  fesoterodine 8 mg;  $p\leq 0.001$ ). Dry mouth was the most experienced adverse effect and was reported significantly more often in the treatment groups (7.1 percent placebo, 16.9 percent tolterodine ER, 21.7 percent fesoterodine 4 mg, and 33.8 percent fesoterodine 8 mg). Overall, 3.2 percent of subjects discontinued the study prematurely owing to an adverse effect (2 percent placebo, 3 percent tolterodine ER, 3 percent fesoterodine 4 mg, and 5 percent fesoterodine 8 mg).

fesoterodine (toviaz) versus tolterodine ER (Detrol LA) versus placebo

A 12-week, randomized, double-blind, double-dummy placebo-controlled, parallel-group multicenter trial with a two-week single-blind placebo run-in period was conducted to assess the efficacy of fesoterodine in comparison to tolterodine ER and placebo.<sup>106</sup> Subjects, at least 18 years of age, with a history of OAB symptoms for at least three months prior to screening and a mean of one or more urgency urinary incontinence (UUI) episodes per 24 hours and eight or more micturations reported in a three-day baseline period, were randomized to fesoterodine 8 mg, tolterodine ER 4 mg, or placebo in a 2:2:1 ratio. A total of 1,712 patients were randomized with 1,697 patients receiving at least one dose of study medication (fesoterodine n= 679; tolterodine ER n=684; placebo n=334). The primary efficacy endpoint was a change from baseline to week 12 in UUI per 24 hours. Both the fesoterodine group and the tolterodine group produced a significantly greater improvement in UUI episodes than the placebo group, ( $p<0.001$  and  $p=0.011$ , respectively). The fesoterodine improvement in UUI compared to the tolterodine ER group was also statistically significant ( $p=0.017$ ). Dry mouth was the most experienced adverse effect and was reported significantly more often in the treatment groups (16 percent for tolterodine ER 4 mg and 28 percent for fesoterodine 8 mg) than placebo (6 percent).

oxybutynin gel (Gelnique) versus placebo

The efficacy and safety of oxybutynin gel were evaluated in single, randomized, double-blind, placebo-controlled, parallel-group, 12-week study for the treatment of overactive bladder (OAB) with symptoms of urge incontinence, urgency, and frequency.<sup>107</sup> Adult patients were included if they had four or more incontinence episodes in a three-day period and at least eight micturations daily. A total of 789 were randomized to receive either oxybutynin gel 1 gm (n=389) or placebo gel (n=400). Each patient had an average duration of urinary incontinence of 8.5 years, and 75 percent of patients had no prior pharmacologic treatment for the condition. Patients treated with oxybutynin gel had a statistically significant decrease in the mean number of urinary incontinence episodes per day from baseline to endpoint compared with placebo (-3 versus -2.5 per day,  $p<0.0001$ ). Dry mouth was reported by 6.9 percent of the oxybutynin gel group compared to 2.8 percent of the placebo group. Application site reactions were observed in 5.4 percent and 1 percent of the oxybutynin gel and placebo-treated groups, respectively.

oxybutynin (Ditropan) versus oxybutynin transdermal (Oxytrol)

A total of 76 patients with detrusor instability who were currently responding to oxybutynin immediate-release were enrolled in a double-blind, dose-titration study.<sup>108</sup> Those patients presenting with recurrence of incontinent symptoms after a two-week washout period underwent confirmatory cystometrogram with subsequent randomization to transdermal or oral oxybutynin treatment. Patients applied two to four transdermal oxybutynin 1.3 mg/day transdermal patches twice weekly or oxybutynin 5 mg orally two or three times daily, plus the alternative placebo dosage form. The initial dose was based on prior dose requirements; subsequent dosages were titrated based on anticholinergic symptoms. More dose increases were tolerated in the transdermal group, with 68 percent of patients reaching the maximum dose compared with 32 percent of patients in the oral group. Daily incontinent episodes decreased in the transdermal group from 7.3 to 2.4 (66 percent reduction) and in the oral group from 7.4 to 2.6 (72 percent reduction;  $p=0.39$ ). The visual analog scale reduction in urinary leakage improved from washout in both groups ( $p<0.0001$ ) with no difference between them ( $p=0.9$ ). Average bladder volume at first detrusor contraction increased by 66 mL in the transdermal group ( $p=0.006$ ) and 45 mL in the oral group ( $p=0.143$ ;  $p=0.57$ ). Dry mouth occurred in significantly fewer patients in the transdermal (38 percent) compared with those in the oral group (94 percent;  $p<0.001$ ). Of the

patients in the transdermal group, 67 percent noticed a reduction in dry mouth severity compared with previous oral treatment. Ten percent of patients in the transdermal group had moderate to severe skin erythema.

### oxybutynin (Ditropan) versus tolterodine (Detrol)

In a randomized, double-blind trial, 378 patients 50 years or older with symptoms of OAB received two weeks of treatment with an initial dose of either tolterodine 2 mg or oxybutynin 2.5 or 5 mg twice daily for eight weeks.<sup>109</sup> Tolterodine and oxybutynin each caused a significant decrease in the mean number of voids per 24 hours, urge incontinence episodes per 24 hours, and mean voided volume after ten weeks of treatment ( $p=0.0001$  for all endpoints). Both agents had comparable efficacy for improving urinary symptoms. Patients treated with tolterodine had significantly fewer adverse events (69 versus 81 percent, respectively,  $p=0.01$ ), notably less dry mouth (37 versus 61 percent,  $p<0.0001$ ), as well as a lower incidence of dose reduction (six versus 25 percent,  $p<0.0001$ ) than those in the oxybutynin group.

### oxybutynin (Ditropan) versus trospium (Sanctura)

In a randomized, double-blind, multicenter trial, 95 patients with spinal cord injuries and detrusor hyperreflexia were evaluated.<sup>110</sup> Treatment consisted of a two-week administration period of either oxybutynin 5 mg three times daily or trospium 20 mg twice daily with an additional placebo at midday. Maximum bladder capacity was increased 97 mL in the trospium group and 163 mL in the oxybutynin group. The increase in maximum bladder capacity was significantly different in both groups compared with baseline ( $p<0.001$ ) but did not differ significantly between groups ( $p=0.057$ ). With both drugs, there was a significant decrease in maximum voiding detrusor pressure and a significant increase in compliance and residual urine compared to placebo; there were no statistically significant differences between the treatment groups. The percentage of patients who reported severe dryness of the mouth was lower in the trospium group (four percent) than in the oxybutynin group (23 percent). Withdrawal from treatment was less frequent in those receiving trospium (six percent) than in those receiving oxybutynin (16 percent).

A total of 358 patients with urge syndrome or urge incontinence were randomized to 52 weeks of treatment with either trospium 20 mg or oxybutynin 5 mg, each given twice daily.<sup>111,112</sup> Analysis of the patient micturition diary indicated a reduction of incontinence frequency and a reduction of the number of urgencies in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 mL after 26 weeks and 115 mL after 52 weeks ( $p=0.001$ ). Micturition frequency was reduced 31 percent with trospium and 34 percent with oxybutynin ( $p=NS$ ). Adverse events occurred in 65 percent of the patients treated with trospium and 77 percent of those treated with oxybutynin ( $p<0.01$ ). Gastrointestinal adverse effects were reported by 39 and 51 percent ( $p=0.02$ ), while dry mouth was reported by 33 and 50 percent ( $p<0.01$ ) of trospium-treated and oxybutynin-treated patients, respectively. Very good tolerability was reported for 63 percent of patients in the trospium group compared with 42 percent of patients in the oxybutynin group ( $p=0.004$ ). The evaluation of vital parameters, laboratory results, and ECGs did not show any relevant changes attributable to the action of the anticholinergics.

### oxybutynin ER (Ditropan XL) versus tolterodine ER (Detrol LA)

The OPERA (OAB: Performance of Extended Release Agents) trial was a multicenter, randomized, double-blind, active-control study. In the study, oxybutynin ER 10 mg per day or

tolterodine ER 4 mg per day were given for 12 weeks to women with 21 to 60 episodes of urge urinary incontinence per week and an average of 10 or more voids per 24 hours.<sup>113</sup> Episodes of urge urinary incontinence, total incontinence, and micturition were recorded in 24-hour urinary diaries at baseline and for 12 weeks. Improvements in weekly urge urinary incontinence episodes were similar for women who received the ER formulations of oxybutynin (n=391) or tolterodine (n=399). Oxybutynin ER was significantly more effective than tolterodine ER in reducing micturition frequency (p=0.003). No episodes of urinary incontinence were reported by 23 percent of women taking oxybutynin ER compared with 16.8 percent of women taking tolterodine ER (p=0.03). Dry mouth, usually mild, was more common with oxybutynin ER (p=0.02). Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events.

### oxybutynin transdermal (Oxytrol) versus tolterodine ER (Detrol LA)

A double-blind, double-dummy trial compared the effects of transdermal oxybutynin with those of tolterodine ER in patients with urge or mixed urinary incontinence who had responded well to prior pharmacologic treatment.<sup>114</sup> After withdrawal of their previous therapy, 361 adult patients were randomized to receive 12 weeks of treatment with oxybutynin 3.9 mg/day transdermal patch twice weekly, tolterodine ER 4 mg daily, or placebo. Both active treatments were significantly more effective than placebo in decreasing the number of daily incontinence episodes, increasing average void volume, and improving QoL. Micturition frequency decreased by a mean of 1.9 episodes per day in the oxybutynin group (p=NS compared to placebo) compared with a decrease of 2.2 episodes per day in the tolterodine ER group (p<0.05 compared to placebo). The most common adverse event for transdermal oxybutynin was localized pruritis occurring in 14 percent of patients and resulting in discontinuation in nearly ten percent of patients. Anticholinergic adverse effects were more common in the tolterodine ER group compared with the oxybutynin group; adverse effects included dry mouth (7.3 and 4.1 percent, respectively) and constipation (5.7 and 3.3 percent, respectively). Dry mouth was significantly more common in the tolterodine ER group than in the placebo group, but the smaller increase of dry mouth in the oxybutynin group was not significantly elevated above placebo. Of those who received tolterodine ER, 1.6 percent discontinued therapy because of fatigue or dizziness. The manufacturer of oxybutynin transdermal patches, which also employed one of the study authors, funded the study.

### solifenacin (VESIcare) versus tolterodine (Detrol)

A multicenter, double-blind trial enrolled 1,281 patients in a tolterodine- and placebo-controlled trial conducted to evaluate the safety and efficacy of solifenacin.<sup>115</sup> Adult patients with symptomatic OAB for at least three months were eligible. After a single-blind, two-week placebo run-in period, patients were randomized to 12 weeks of treatment with either solifenacin 5 or 10 mg once daily, tolterodine 2 mg twice daily, or placebo. In the 1,033 patients evaluated for efficacy, the change from baseline in the mean number of urgency episodes per 24 hours was lower with solifenacin 5 mg (-2.85; p<0.001) and 10 mg (-3.07; p<0.001), but not with tolterodine (-2.05; p=0.051). There was not a statistically significant decrease in episodes of incontinence with tolterodine (-1.14; p=0.112) but a significant decrease in patients treated with solifenacin 5 mg (-1.42; p=0.008) and 10 mg (-1.45; p=0.0038). Compared with placebo, the mean number of voids per 24 hours was significantly lower in patients receiving tolterodine (-1.88; p=0.0145), solifenacin 5 mg (-2.19; p<0.001), and 10 mg (-2.61; p<0.001). The mean volume per void was significantly higher with all three active treatments (p<0.001). The most common adverse effect, dry mouth which was mostly mild, was reported in 18.6 percent of patients receiving tolterodine, 14 percent receiving solifenacin 5 mg, and 21.3 percent receiving solifenacin 10 mg.

solifenacin (VESIcare) versus tolterodine ER (Detrol LA)

The STAR trial (Solifenacin and Tolterodine extended-release as an Active comparator in a Randomized trial) was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine ER 4 mg once daily in patients with OAB.<sup>116</sup> After the first four weeks of therapy, patients could request a dose increase, but the blinding was maintained since a dose increase was only allowed for the solifenacin-treated group. More of the solifenacin-treated patients showed reduced urgency episodes, incontinence, urge incontinence, pad usage, and increased volume voided per micturition. Also, the majority of adverse effects were mild with a low discontinuation rate for both groups.

tolterodine (Detrol) versus tolterodine ER (Detrol LA)

In a placebo-controlled safety and efficacy evaluation, 1,529 patients with urinary frequency (eight or more micturitions every 24 hours) and urge incontinence (five or more episodes per week) were randomized in a double-blind fashion to tolterodine ER 4 mg once daily, tolterodine 2 mg twice daily, or placebo.<sup>117</sup> Efficacy was assessed at the end of the treatment period on the basis of the micturition diary variables. Tolerability and safety were assessed by evaluating the adverse events, electrocardiogram parameters, laboratory values, and treatment withdrawals. Both active dosage forms significantly decreased the number of urge incontinence episodes per week (by 71 and 60 percent, respectively) compared to placebo (33 percent). Micturition frequency decreased and volume increased in both tolterodine groups. The incidence of dry mouth was 23 percent in the tolterodine ER group, 30 percent in the tolterodine group, and eight percent in the placebo group. Of the 1,377 patients completing the study, 1,077 chose to continue with 12 months of open-label treatment with tolterodine ER 4 mg once daily.<sup>118</sup> During the 12-month treatment period, efficacy of tolterodine ER was maintained, and there was no increase in the frequency of adverse events relative to the short-term treatment.

tolterodine (Detrol) versus trospium (Sanctura)

Trospium was compared with tolterodine in a double-blind, placebo-controlled study enrolling 234 patients with urgency or urge incontinence.<sup>119</sup> Patients were randomly assigned therapy with either 20 mg trospium, 2 mg tolterodine, or placebo, each given twice daily for three weeks. In the 180-patient population, micturition frequency was reduced by 3.4 episodes per 24 hours in the trospium group, 2.6 episodes in the tolterodine group, and 1.9 episodes in the placebo group. Adverse events occurred with similar frequency in the trospium and tolterodine groups.

trospium ER (Sanctura XR) versus placebo

A multicenter, double-blind, placebo-controlled study enrolled 601 patients with OAB symptoms into a 12-week study.<sup>120</sup> Patients were randomly assigned to therapy with either trospium ER 60 mg or placebo given once daily. Primary endpoints included change in daily urinary frequency and urgency urinary incontinence episodes. Secondary end points were urgency severity, volume voided per void, and the number of urgency voids per day. Safety was assessed by clinical examination, adverse event monitoring, clinical laboratory values and resting electrocardiograms. Patients (n=298) in the trospium ER group showed a statistically significant (p<0.01) improvement over the placebo (n=303) group in all primary and secondary outcomes at week one through week 12. The most common adverse events were dry mouth (trospium 8.7 versus placebo three percent) and constipation (trospium 9.4 percent versus placebo 1.3 percent). Central nervous system adverse events were rare (headache with trospium one

percent versus placebo 2.6 percent). No clinically meaningful changes in laboratory, physical examination, or electrocardiogram parameters were noted.

### Summary

In comparative trials with tolterodine (Detrol), tolterodine ER (Detrol LA), trospium (Sanctura), and oral oxybutynin formulations have been associated with greater incidences of anticholinergic adverse effects, but were otherwise as effective as the comparators. The transdermal oxybutynin medications (Gelnique, Oxytrol) appear to cause fewer anticholinergic adverse effects, likely by avoiding first-pass metabolism to N-desethyloxybutynin, an active metabolite partly responsible for such effects. However, both the gel and transdermal patches are associated with a relatively high rate of cutaneous reactions, which can result in discontinuation of the agent.

There is no ideal agent within this class. Head-to-head studies reveal little to no difference in efficacy among these agents, and there are little to no variations among subpopulations within studies. Furthermore, those studies where immediate-acting agents were compared to their extended-release counterparts found no important differences in efficacy and only statistical variations in adverse effects. The agents in this class may be considered therapeutically interchangeable with the final selection depending on patient specifics and tolerance.

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